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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,740	08/16/2006	James Van Alstine	PU0407	9504

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EXAMINER	
KETTER, JAMES S	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,740	VAN ALSTINE ET AL.	
	Examiner	Art Unit	
	James S. Ketter	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 9-13, 15, and 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Musil et al. (cited in IDS filed 16 August 2006 as reference B1).

Claim 1 is drawn to a method of isolating at least one plasmid from other component(s) of a liquid, comprising providing a separation matrix comprised of one or more porous carriers, which carrier(s) present anion exchange groups on external surfaces as well as pore surfaces and a pore size distribution that does not allow access of plasmids to pore surfaces, contacting said matrix with the liquid to adsorb the plasmid(s) to ligands present on the external surfaces of the separation matrix and, optionally, contacting an eluent with the separation matrix to release the plasmid(s) and recovering plasmid(s) from a fraction of said eluent. Claim 2 is drawn to a method of isolating at least one plasmid from other component(s) of a liquid, comprising providing a separation matrix comprised of one or more porous carriers, which carrier(s) present anion exchange groups on external surfaces as well as pore surfaces and a DNA exclusion limit of at least about 270 base pairs, contacting said matrix with the liquid to adsorb the plasmid(s) to ligands present on the external surfaces of the separation matrix and, optionally, contacting an eluent with the separation matrix to release the plasmid(s) and recovering plasmid(s) from a fraction of said eluent. Claim 3 specifies within claim 2 that the DNA exclusion limit of the

separation matrix is at least about 1,000 base pairs. Claim 4 specifies within claim 1 or 2 that the separation matrix is in the form of essentially spherical particles having an average diameter of 30-50 μm. Claim 5 specifies within claim 1 or 2 that the plasmids are of a size that exceeds about 3,000 base pairs. Claim 6 specifies within claim 1 or 2 that the method is a large scale process wherein at least about 1 grams of plasmid is recovered. Claim 9 specifies within claim 1 or 2 that the method further comprises subjecting the plasmid-containing eluate to hydrophobic interaction chromatography (HIC). Claim 10 specifies within claim 1 or 2 that said anion-exchange groups are selected from the group consisting of quaternary amine (Q) groups and diethylamine groups. Claim 11 is drawn to a separation matrix for the purification of plasmids comprisin~ one or more porous carriers which carrier(s) present anion exchange groups on external surfaces as well as pore surfaces and a pore size distribution that does not allow access of plasmids to pore surfaces. Claim 12 is drawn to a separation matrix for the purification of plasmids comprising a porous carrier wherein anion-exchange groups have been immobilized on the surfaces, which matrix presents a DNA exclusion limit of at least about 270 base pairs. Claim 13 specifies within claim 12 that the DNA exclusion limit of the matrix is at least about 1,000 base pairs. Claim 15 specifies within claim 11 or 12 that the separation matrix is in the form of essentially spherical particles having an average diameter of 30-50 μm, and the plasmids are of a size that exceeds about 3,000 base pairs. Claim 17 specifies within claim11 or 12 that the volumes exceed about 1 grams of plasmid. Claim 18 is drawn to a kit comprising, in separate compartments, a separation matrix comprised of one or more porous carriers, which carrier(s) present anion exchange groups on external surfaces as well as pore surfaces and a pore size distribution that does not allow access of plasmids to pore surfaces; at least one buffer; and

written instructions that describes how plasmids are purified from other components of a liquid using said kit. Claim 19 is drawn to a kit comprising, in separate compartments, a separation matrix comprised of a carrier to the surfaces of which anion-exchange groups have been immobilised, which matrix presents a DNA exclusion limit of at least about 270 base pairs; at least one buffer; and written instructions that describes how plasmids are purified from other components of a liquid using said kit. Claim 20 specifies within claim 19 that the DNA exclusion limit of the matrix is at least about 1,000 base pairs. Claim 21 specifies within claim 18 or 19 that the matrix is in the form of essentially spherical particles having an average particle diameter of 30-50 μm. Claim 22 specifies within claim 18 or 19 that the separation matrix is provided in a chromatography column the diameter of which is at least about 10 cm.

Musil et al. teaches, e.g., at pages 7 and 8, that

> "the invention employs a trimethylaminoethyl (TMAE) fractogel anion exchange resin. The resin is packed into a standard, preferably large- scale column, such as a Pharmacia XK 50 column, at a suitable bed height (e.g., approximately 20.5 cm) and a suitable total column volume (e.g., approximately 400 ml). The column is then run on a suitable preparative HPLC at a linear flow rate of e.g., 150 crn/hr. Chromatographic profiles are then monitored at two different wavelengths, for example, 260 nm and 280 nm, and peak fractions collected based on their real time chromatographic profiles. Following packing, the column is equilibrated and the sample containing the plasmid DNA is loaded onto the column. Typically, the first wash contains relatively high salt (e.g., 0.68 M NaCl) and results in selective binding of components contained in the sample to the column, and removal of most of the detergent. This optional wash is then followed by a stringent alcohol (e.g., ethanol) wash which removes both endotoxins bound to the column, and any residual detergent (e.g., Triton X-114), without removing plasmid DNA bound to the column. The term "stringent", as used herein, means a concentration of organic solvent (e.g., alcohol) of between 25% and 90%, more preferably approximately 40%. While ethanol is the preferred alcohol for use in the stringent wash, other alcohols know in the art, such as methanol, also can be used. The stringent wash also preferably contains a smaller percentage of a neutralizing acid, such as acetic acid. When using ethanol at the preferred concentration of about 5%, acetic acid is preferably present in the wash at a concentration of about 40%. The column is then finally eluted to capture the remaining plasmid DNA bound to the column."

TMAE is a porous anion exchange resin. At page 12, lines 13-25, the plasmid is taught as a pUC19 inserted with the coding region of human IFN-alpha2b gene plus an additional 390 bp, thus meeting all of the claimed size exclusion limitations. At page 3, lines 4 and 5, it is taught that the process may be operated at large scale.

Claims 1-13 and 15-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Nochumson et al. (A, newly cited).

Claims 1-6, 9-13, 15, and 17-22 are described above. Claim 7 specifies within claim 1 or 2 that one of the other components of the liquid is RNA which is adsorbed to ligands present on the pore surfaces of the separation matrix. Claim 8 specifies within claim 7 that the plasmids that are recovered are essentially free from RNA. Claim 16 specifies within claim 11 or 12 that the pore surfaces of the separation matrix absorb RNA impurities, while the external surfaces of the separation matrix absorb the plasmids.

Nochumson et al. teaches, e.g., at column 4, fourth full paragraph, and the three subsequent paragraphs, that

"[t]he invention relies, in part on the use of anion exchange chromatography, preferably with a Fractogel EMD 650S TMAE(S) resin with a 20 40 micron size. Other tentacle resins or means for making binding sites more available to larger molecules like plasmids can also be used. The tentacles are prefrrably 15 to 50 units in length and have an average of 18 charged groups covalently bound to each tentacle. TMAE Fractogel 650S is a tentacle ion exchanger having trimethylaminoethyl functional groups (TMAE) covalently attached to hydroxyl groups of a synthetic methacrylate based polymeric resin backbone.

The use of such resins: (1) provides a high plasmid DNA binding capacity (about 3 mg/mL, preferably about 1.5 mg/mL); (2) allows for efficient removal of proteins, RNA, low molecular weight molecules and probably some chromosomal DNA and some open circle

plasmid DNA; and (3) provides a means for enriching the supercoiled plasmid DNA above about 80% using a step gradient. Supercoiled plasmid binds tighter to the Fractogel resin (high affinity sites) allowing the remaining RNA and some open circle plasmid to be removed.

The invention also relies in part on the use of hydrophobic interaction chromatography, which is used to separate plasmid DNA from E. coli chromosomal DNA and RNA and may also be used to separate open circular plasmid DNA from supercoiled DNA. Overall, HIC is a powerful technique for plasmid DNA purification. This disclosure reveals the surprising and unexpected value that hydrophobic interaction chromatography (HIC) has, especially when used in conjunction with anion-exchange chromatography, for large-scale plasmid DNA purification. Particularly surprising is the ability of HIC to resolve the supercoil form of a plasmid from the relaxed open circle form. Supercoiled DNA may be easier to formulate and with certain formulations supercoiled plasmid may have higher expression levels in vivo (e.g., about 10 times greater expression in certain systems). Another surprising and important fact is that removal of chromosomal DNA, denatured plasmids, RNA, and endotoxin from the plasmid DNA forms can also be achieved.

Thus, in one aspect the invention provides a process for isolating a large quantity (e.g. gram or kg amounts) of plasmid DNA. The method involves the steps of: (a) lysing cells containing the plasmid DNA with a lysis agent, thereby forming a lysate; (b) treating the lysate with a high salt agent that preferably is capable of forming a precipitable complex with non-plasmid DNA cellular components contained in the lysate, thereby forming a treated solution; and (c) purifying the treated solution to provide isolated plasmid DNA."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James S. Ketter whose telephone number is 571-272-0770. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JSK
10 March 2009

/James S. Ketter/
Primary Examiner, Art Unit 1636